Remarks

Prior to entry of this filing, claims 1-15 were pending of which claims 5-12 are withdrawn as being directed to non-elected subject matter. Claim 15 is amended to correct a clerical error; new claim 16 is added. The new claims are supported in the specification and claims as originally filed; no new matter is added by this amendment.

After entry of this amendment, claims 1-16 are pending (of which claims 5-12 remain withdrawn). Reconsideration, rejoinder, and allowance of the claims are respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 1-4 and 13-15 were rejected as allegedly obvious over Zhang *et al.* (1994) in view of Modin *et al.* (2001). Applicants traverse.

The Office has not Properly Established a Prima Facie Case of Obviousness

Applicants respectfully submit that Zhang *et al.*, Modin and Nachtsheim fail to satisfy the requirements for a finding of obviousness of claims 1-4 and 13-15, in accordance with the requirements of the "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" (72 Fed. Reg. 57526-57535, October 10, 2007) (the "Guidelines"). In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 at 17-18 (1966), the Supreme Court set out the following objective framework for applying the statutory language of §103:

> "Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

Accordingly, the Guidelines confirm that obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court in *Graham* are:

(1) Determine the scope and content of the prior art;
(2) Ascertain the differences between the claimed invention and the prior art; and
(3) Resolve the level of ordinary skill in the pertinent art.

The Office characterizes the content of the cited references as follows: Zhang *et al.* teach the use of nitric oxide (NO) donors (that is, sodium nitroprusside and 3-morpholino-sydnonimine) to increase blood flow and reduce brain damage due to focal ischemia; and Modin teaches that (i) NO is derived from nitrite (citing the title of Modin) and (ii) non-acidified nitrite "has relaxatory effects similar to "acidified" nitrite" (citing figures 1, 2, and 5, and the accompanying text. According to the Office, the only difference between the instant application and Zhang *et al.* is an express teaching of non-acidified sodium nitrite in the amount of 0.6 to 240 μM, which deficiency is allegedly cured by Modin *et al.*

With respect to the first and second of the *Graham* factual inquiries, Applicants respectfully submit that the Office has not properly determined the scope and content of the cited references, and because of this has overlooked important differences between the claimed invention and the cited references. Applicants further respectfully note that these differences overlooked by the Office are significant, because they dictate that there could have been no reasonable expectation that one of ordinary skill in the art could have predictably reached Applicants' invention based on the teachings of the cited references in view of the prior art as a whole.

The Guidelines provide the following non-exclusive rationales for supporting a finding that a claimed invention is obvious (emphasis added), which rationales have subsequently been incorporated in the M.P.E.P. at § 2143:

(A) combining prior art elements according to known methods to yield **predictable** results;

(B) simple substitution of one known element for another to obtain **predictable** results;

(C) use of known technique to improve similar devices (methods, or products) in the same way;

(D) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "obvious to try" - choosing from a finite number of identified, **predictable** solutions, **with a reasonable expectation of success**;

(F) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been **predictable** to one of ordinary skill in the art; and

(G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The emphasis in the Guidelines is accordingly the **predictability** of the combination of elements from the prior art, as a basis for a finding that there is a reasonable expectation of success associated with a prior art combination. It is respectfully submitted that in the present case, there is **no such element of predictability in the purported combination of prior art references, and accordingly no reasonable expectation of success**. Thus, the obviousness rejections cannot stand.

"Nitric oxide donors" (as that phrase is used in Zhang *et al.*) are different from inorganic nitrites (salts), such as sodium nitrite. The only difference the Office points out between Zhang *et al.* and the present invention is that Zhang does not teach non-acidified sodium nitrite in the amount of 0.6 to 240 μM. The Office then states that this defect is cured by Modin. By doing so, the Office overlooks significant distinctions between Zhang and Modin, as well as the present invention: **"nitric oxide donors" and sodium nitrite are not equivalent substitutes for each other**.

Zhang *et al.* describe use of sodium nitroprusside (SNP) and 3-morpholino-sydnonimine (SIN) in experiments with rats. Applicants' claims, and the work described by Modin, employ sodium nitrite, *i.e.*, an inorganic nitrite. Nitric oxide donors and inorganic nitrite are structurally dissimilar and they form NO in different manners. SNP and SIN release NO directly whereas sodium nitrite interacts with heme to form NO *in* vivo. In addition, the molecular formulas for each are quite distinct:

Sodium nitrite	$NaNO_2$
SNP	$Na_2[Fe(CN)_5NO]\cdot 2H_2O$
SIN	$C_6H_{11}N_4O_2\cdot Cl$

The Office must provide evidence that one of ordinary skill would have had a reasonable expectation that an inorganic nitrite salt (such as sodium nitrite) is an equivalent substitute for the structurally dissimilar SNP or SIN. No such evidence is on record, nor do Applicants know of any such evidence. In fact, it was recognized in the art many years before Applicants' filing that different NO producing compounds have different effects and work by different mechanisms; see Wanstall *et al.* (*Brit. J. Pharma.* 134:463-472, 2001), a copy of which is provided herewith as Exhibit A. For

instance, at the start of the last paragraph on page 470 of Wanstall *et al.*, the authors state "The data in this study have highlighted the heterogeneity in the pharmacological profiles of each of the six NO-producing agents." The authors conclude in the paragraph on page 471 as follows: "The findings of this study emphasise that one should give careful consideration to the choice of NO donor..."

Nothing on the record indicates that the art had an expectation of similar properties for these compounds. Neither Zhang *et al.* nor Modin equate the activities of sodium nitrite to SNP or SIN, nor do these references teach the interchangeability of these diverse compounds. There is no art-recognized equivalence between these compounds, for any purpose. The Office has not placed any such evidence on record, nor do Applicants know of any such evidence – and in fact the art has long recognized that different "nitric oxide donors" behave differently.

In view of this, and given the significantly different structures and different mechanisms of generating (or releasing) NO, the Office must provide evidence that one of ordinary skill would have a reasonable expectation that sodium nitrite could be used as an equivalent substitute for SNP or SIN. Contrary to the position taken by the Office, one of skill in this art would *not* have had a reasonable expectation that the inorganic nitrite of Modin could successfully substitute for the nitric oxide donors used by Zhang because (as explained below) the results of Modin are not applicable to an *in vivo* system and this too was recognized by the art at the time of Applicants' filing.

Thus, another significant difference between the cited references and Applicants' invention that has been overlooked by the Office is that the studies of Modin were conducted in aortic ring bioassays **without circulating blood**, in contrast to Applicants' methods. The Modin studies are qualitatively not different from similar work performed by Robert Furchgott in 1952 (Furchgott & Bhadrakom, *J Pharmacol Exp Ther* 108(2):129-43, 1953, previously made of record). These experiments were all performed in **isolated** aortic rings **without blood in them**. Because these studies required non-physiological conditions – extremely low oxygen tension and low pH, as well as high nitrite concentrations – they were not considered by those of skill in the art to reflect what would happen in the human circulation. Thus, there would be no reasonable expectation that sodium nitrite as employed in Modin would predictably function in the methods provided in Zhang – that is, there was no reasonable expectation that sodium nitrite would work in vivo in the presence of blood. This was

clearly evinced by the Lauer paper – which clearly concluded that "nitrite lacks intrinsic vasodilator action" (see below). One of skill in the art, prior to Applicants' invention, would have expected that the presence of blood would have **inhibited** the NO generated from nitrite, not increased it.

It has now been clearly shown by Isbell *et al.* (*Am J Physiol Heart Circ Physiol* 293(4):H2565-72, 2007) that oxygenated blood inhibits the nitrite induced vasodilation of aortic rings; a copy of Isbell *et al.* was previously provided to the Office in this file. Thus, it is very clear that the results of *in vitro*, blood-free experiments such as described in Modin are not applicable to an *in vivo* situation. See also Crawford *et al.* (*Blood* 101:566-574, 2006; previously made of record in this file), where the authors conclude that their "data support a function for RBC hemoglobin as an allosterically and redox-regulated nitrite reductase whose "enzyme activity" couples hypoxia to increased NO-dependent blood flow." (Crawford *et al.*, Abstract.)

In addition, Modin itself teaches away from Applicants' invention. As indicated in Section 2141.02 of the MPEP, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including those portions that would lead away from the claimed invention. (*W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). Modin teaches that **acidified** inorganic nitrite is preferred, and therefore that non-acidified inorganic nitrite is **not** preferred. The clear teaching of Modin, as acknowledged in the Office's summary of Modin, is that inorganic nitrite is a more effective vasodilator in an acidic environment as compared to a non-acidic environment. Thus, if one of ordinary skill in this art were to consult Modin in relation to Zhang, the only potentially reasonable conclusion to draw from Zhang would be to use the "nitric oxide donor" in an acidic environment, as it is more efficient and effective.

Even if, for the sake of argument, the compound used by Modin was deemed a reasonable substitute to the compound used by Zhang (which Applicants do not admit), there is no credible support for an allegation that one of skill would have used the (allegedly) non-acidified sodium nitrite of Modin in the method of Zhang. This is more than a "mere disclosure of more than one alternative" (MPEP 2141.02), but instead is a clear teaching away that criticizes, discredits, or otherwise discourages the solution claimed by Applicant. See *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

It is respectfully submitted that in the present case, the Office has not demonstrated that one of ordinary skill in the art would have had a **predictable and reasonable expectation of success in combining the teachings of the cited references** (Zhang and Modin) to yield Applicants' invention. Thus, the obviousness rejections cannot stand.

Secondary Evidence of Non-Obviousness

Even if the Office had generated a proper *prima facie* case of obviousness (which Applicants do not concede), secondary indicia of non-obviousness are present that refute the alleged obviousness of Applicants' claims.

Section 2145(X)(D)(3) of the MPEP explicitly recognizes that "proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)." Furthermore, "[k]nown disadvantages… which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

The art prior to Applicants' invention taught that **inorganic nitrite (particularly sodium nitrite) did not have vasodilatory effect *in vivo***. Art available as of the priority date of the present application taught that administration of pharmaceutical levels of nitrite to human subjects *in vivo* did not induce vasodilation and/or increase blood flow. This is discussed, for instance, at page 2, lines 4-13 and page 21, lines 29-33 of Applicants' specification.

Because of the low potency of nitrite in aortic rings without acidification (see, *e.g.*, Modin and Furchgott), and the effects of blood on inhibiting NO, the state of the art as of the priority date of Applicants' filing was that nitrite was not a vasodilator in the human circulation system, particularly at concentrations less than 200 μM. This is made abundantly clear in the Lauer study (Lauer *et al.*, *PNAS* 98:12814-12819, 2001). Even the title of the Lauer study claims that "nitrite lacks intrinsic vasodilator action". On page 12816, at the bottom right paragraph, the authors indicate: "Intraarterial application of nitrite was found to be devoid of vasodilator activity at doses up to 36 μM/minute. Venous plasma nitrite concentrations achieved at the highest dose level exceeded 130 μM and were thus approximately

200 times greater than the concentrations measured during maximal eNOS stimulation with Ach." On page 12818 at the bottom right, the authors further claim: "The complete lack of vasodilator activity of intraarterial infusion of nitrite clearly rules out any role for this metabolite in NO delivery."

Further, Lauer *et al.* concluded that "[i]ntraarterial application of nitrite ($NaNO_2$ in 0.9% saline) was found to be devoid of vasodilator activity at doses up to 36 μmol/min (tested range: 0.01-36 μmol/min; n = 3)" (Lauer at page 12816, right column, last paragraph). Similarly, Rassaf concluded that "…the application of exogenous nitrite and nitrate at doses equimolar to those of NO did not exert dilation at all…" (Rassaf *et al.*, *J. Clin. Invest.*, 109:1241-1248, 2002, at page 1245, 1st column, 2nd paragraph). (Copies of both Lauer and Rassaf were previously made of record in this file.)

Thus, one of skill in the art reading Lauer, Rassaf and Modin, would conclude that **aortic ring bioassays** are a poor system in which to study or characterize the *in vivo* vasodilatory effects of sodium nitrite – because the *in vitro* aortic ring bioassays lack blood (and particularly heme), they are not predictive of the *in vivo* situation.

Further, based on the *in vivo* teachings of Lauer and Rassaf related to inorganic nitrite and vasodilation, the skilled artisan would not have expected sodium nitrite to have any beneficial therapeutic effect when administered (for instance by injection or inhalation) to a subject to induce vasodilation or increase blood flow, regardless of the *in vitro* results in rat aorta provided by Modin. This was the accepted state of the art of the field at the time of Applicants' filing. This is evidenced further by Applicants' research corresponding to the subject application having been published in *Nature Medicine* – such publication **requires** that the research be new for it to be published.

Applicants also note that there was strong resistance in the art to their work, approaching the level of ridicule by others in the field – reflective of there being absolutely nothing obvious about Applicants' invention. See, for instance, the set of Letters to the Editor published in *The New England Journal of Medicine* on July 24, 2003 (349:402-405; provided to the Office previously), comment on Applicants' earlier work (Schechter & Gladwin, *N Engl J Med* 348:1483-1485, 2003). By way of example, McMahon (at page 403) indicates "The suggestion that nitrite (at native concentrations) causes vasodilation in humans has been refuted experimentally." (Citing Rassaf *et al.*, 2002). See also

Pawlowski (at page 403), which states that "the latter [nitrite ions] has been shown to lack vasoactivity under physiologic conditions." (Citing Lauer *et al.*, 2001). It is clear on the record that those of ordinary (and expert) skill in the art **did not consider sodium nitrite, or any other inorganic nitrite salt, to have *in vivo* vasodilatory activity**.

Given the above arguments, Applicants assert that the combination of Zhang and Modin does not make the present invention obvious. These references do not provide any reasonable expectation to one of ordinary skill that they could carry out Applicants' invention. Applicants request the withdrawal of the rejection of claims 1-4 and 13-15 as allegedly obvious.

Double Patenting Rejection

Claims 1-4 and 13-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly these claims are unpatentable over claims 1, 6-13 and 20-23 of copending Application No. 10/563,682. Without admitting to the properness of this rejection, Applicants ask that it still be held in abeyance until the claims of one case or the other are allowed. Applicants will provide the Examiner with copies of any prosecution documents from Application No. 10/563,682 on request, though it is noted that the prosecution documents are available on PAIR.

Request for Rejoinder of Species

Based on the finding of Lack of Unity – Species dated August 5, 2008, Applicants understand that those claims directed to non-elected species will be rejoined and examined in the present application upon allowance of a claim generic for the species. Such action is respectfully requested.

Conclusion

In view of the foregoing, Applicants believe the pending claims are in condition for allowance, which action is courteously requested.

If any issues remain, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being

submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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